April 1, 1951.

Dear Paul-

I was, of course, sorry to learn of the disappointing outcome of your NRC application. However, this might have been due in part to your suggested program which the committee conceivably might have reviewed with some hesitancy.

If there is any reasonable possibility of success, by all means follow up with the AEC application. It might be well to emphasize the function of your fellowship in familiarizing yourself with the methodology of microbial genetics, rather than the specific value of the research project. However, we have recently undertaken a very small contract with AEC to study the effects of radiations on (heterozygous diploid) bacteria, and there would be some opportunity for collaboration on this program. On the other hand, I would prefer that you not be tied to this project, which I am planning to keep on a small scale for the time being.

Your last letter also asked for some discussion of your project on strain relationships. I have not hastened to answer in order to give it some thought, and also because the May 1 deadline is still some time off. The basis of the plan is the isolation of a dozen or so new strains (so far, still coming in) of E. coli which can be intercrossed with K-12, and possibly with each other. These cultures show a considerable range of overt phenotypic differences, including reaction to bacteriophages and colicins, production of these agents, fermentation of certain carbohydrates (especially lactose and sucrose), nutritional status, and finally serological structure. Another fellow is planning to analyse the serological differences, which are quite marked: each of the first 10 has a distinct somatic antigen, and some are new additions to the long list of E. coli somatic antigens. I would recommend a project based upon the cataloguing of the overt characteristics of the crossable strains, comparing their range with that of the taxonomic description of E. coli; determining the genetic bases of the differences (e.g. are the different sucrose-negative types the same, single-gene mutation?), and finally looking for cryptic genetic differences as reflected by the occurrence of new characteristics from crosses of parents which are superficially alike in respect to a given character. The last might be of some importance in indicating the extent of latent genetic variability which recombination can expose. Finally, the gene differences detected in the new isolates should be correlated with the experimentally produced mutations in the laboratory (e.g. lactose-negative "paracolon" with particular Lac- mutations in strain K-12).

Let me know if you need some more information. Part of the program should also include an extension, and preferably an expansion, of the routine of finding new crossable strains, especially designed to detect compatibility groups if possible. Enclosed is a letter of endorsement which you may need for your AEC application.

Joshua Lederberg